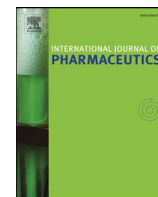




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Potential anticancer activity of protocatechuic acid loaded in montmorillonite/Fe₃O₄ nanocomposites stabilized by seaweed *Kappaphycus alvarezii*

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ABSTRACT

Superparamagnetic magnetite nanocomposites (Fe₃O₄-NCs) were successfully synthesized, which comprised of montmorillonite (MMT) as matrix support, *Kappaphycus alvarezii* (SW) as bio-stabilizer and Fe₃O₄ as filler in the composites to form MMT/SW/Fe₃O₄-NCs. Nanocomposite with 0.5 g Fe₃O₄ (MMT/SW/0.5Fe₃O₄) was selected for anticancer activity study because it revealed high crystallinity, particle size of 7.2 ± 1.7 nm with majority of spherical shape, and M_s = 5.85 emu/g with negligible coercivity. Drug loading and release studies were carried out using protocatechuic acid (PCA) as the model for anticancer drug, which showed 19% and 87% of PCA release in pH 7.4 and 4.8, respectively. Monolayer anticancer assay showed that PCA-loaded MMT/SW/Fe₃O₄ (MMT/SW/Fe₃O₄-PCA) had selectivity towards HCT116 (colorectal cancer cell line). Although MMT/SW/Fe₃O₄-PCA (0.64 mg/mL) showed higher IC₅₀ than PCA (0.148 mg/mL) and MMT/SW/Fe₃O₄ (0.306 mg/mL), MMT/SW/Fe₃O₄-PCA showed more effective killing towards tumour spheroid model generated from HCT116. The IC₅₀ for MMT/SW/Fe₃O₄-PCA, MMT/SW/Fe₃O₄ and PCA were 0.132, 0.23 and 0.55 mg/mL, respectively. This suggests the improved penetration efficiency and drug release of MMT/SW/Fe₃O₄-PCA towards HCT116 spheroids. Moreover, concentration that lower than 2 mg/mL MMT/SW/Fe₃O₄-PCA did not result any hemolysis in human blood, which suggests them to be ideal for intravenous injection. This study highlights the potential of MMT/SW/Fe₃O₄-NCs as drug delivery agent.

1. Introduction

Cancer has been humans' greatest concern as cancer is among the dominant causes of death worldwide and the rate of people diagnosed cancer is increasing nowadays. According to the International Agency for Research on Cancer, the statistic reported by GLOBOCAN expected 18.1 million of new cancer cases and 9.6 million cases of cancer deaths in 2018 globally (Bray et al., 2018), which showed an increment as compared to year 2012 (about 14.1 million new cancer cases diagnosed and 8.2 million deaths) (Torre et al., 2015). Humans are aware of cancer and they practice healthy lifestyle to reduce the risk of getting cancer, but no one can predict it as cancer is difficult to be detected and usually found at the late stage. Hence, new effective cancer screening

and diagnosis approaches as well as cure for cancer are highly demanded to solve this critical disease, so as the number of human deaths due to cancer can be reduced.

In recent years, scientists have made a major breakthrough in medical field, which is the application of nanotechnology in medicine. The implementation of inorganic materials in drug delivery study becomes popular, particularly magnetite (Fe₃O₄) nanoparticles, such as in treating prostate cancer (Singh et al., 2019), lung, breast and colon cancer (Rosman et al., 2018) and cervical cancer (Malekzadeh et al., 2017). Fe₃O₄ is the only magnetic nanoparticles that is recognized by US Food and Drug Administration (FDA) for clinical use (Wang et al., 2010). For instance, Fe₃O₄ has been used in magnetic resonance imaging (MRI) contrast agent (Patsula et al., 2016) and magnetic

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